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14. ABSTRACT

Background: There is a high rate of comorbidity with alcohol dependence (AD) and post traumatic stress disorder (PTSD). The rates of TSD among individuals with AD are at least twice as high as those in the general population. In addition, alcohol dependence is the most common comorbid condition in men with PTSD. Despite this, little is known about how to best treat individuals with comorbid AD and PTSD. The use of an alpha-1 adrenergic receptor antagonist represents a novel approach to treatment that may target symptoms of both AD and PTSD. There is evidence of common neurobiological mechanisms that underlie both AD and PTSD. Prazosin is an alpha-1 adrenergic receptor antagonist that has been used successfully in the treatment of trauma nightmares and sleep disturbance in combat veterans with TSD, and alcohol dependence.

Objective: The objective of this study is to evaluate the efficacy of prazosis (16mg) versus placebo in reducing alcohol consumption and decreasing symptoms of PTSD in patients with comorbid AD and PTSD. Methods: One hundred and twenty participants with a current diagnosis of AD and PTSD will be enrolled in a 13-week trial. They will be assigned, in a double-blind fashion, to either prazosin or placebo. Findings: No fmdings are yet available for this study. Significance: This project will be the first to compare prazosin to placebo as effective treatments for reducing alcohol consumption and PTSD symptoms in patients with both AD and PTSD.

15. SUBJECT TERMS-
PTSD, alcohol dependence, treatment, Prazosin

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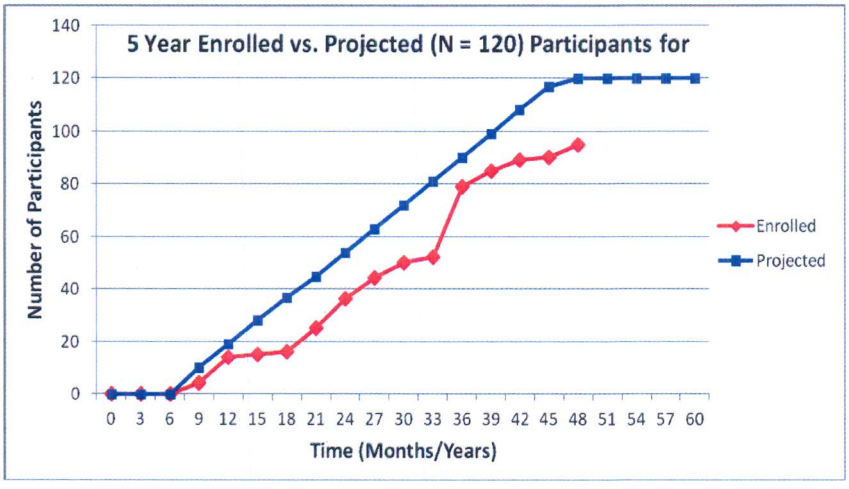
INTRODUCTION: The objective of this research was to evaluate the efficacy of prazosin 16mg versus placebo in reducing alcohol consumption and decreasing symptoms of PTSD in patients with comorbid AD and PTSD. We hypothesized that prazosin will significantly reduce the number of drinking days and reduce the symptoms of PTSD compared to placebo in patients with AD and PTSD. This was a double-blind, multi-site, randomized, 13-week, treatment trial. The recruitment for this study was planned for 4 years but required two additional 1-year no cost extensions (NCE). A third 3-months no cost extension to finish data analysis was also approved.

BODY: This report covers the period of the third no-cost extension. Our goals for this period were to: complete subject recruitment and follow up of all patients recruited in the study, complete data entry, organize and clean the data, prepare the data for statistical analyses, analyze the data, began work on the manuscript. The goals for this year have been accomplished. In addition, we are pleased to report that the manuscript with the figures of the data has been written and is ready for submission for publication. The figure and table below summarize the final subject recruitment.



Included in this report is a table that outlines our final recruitment – at both sites.

Site	# Ss that have signed consent	# Ss enrolled	Ratio of Ss to target
West Haven	124	41	41/72
Bedford	88	55	55/60

KEY RESEARCH ACCOMPLISHMENTS: The recruitment for this study is now complete and the main data analysis has been completed. The manuscript is currently being prepared for publication.

REPORTABLE OUTCOMES:

1. Please see the attached manuscript.
2. A previous manuscript entitled "Characteristics and drinking patterns of veterans with alcohol dependence with and without post-traumatic stress disorder" was published in the journal of "Addictive Disorders". The paper explored differences in the pretreatment characteristics of veterans with alcohol dependence alone compared to those with co-occurring alcohol dependence and posttraumatic stress disorder. Those with co-occurring illnesses demonstrated significantly higher pre-treatment pathology across all psychopathological domains. Those with alcohol dependence alone averaged more days of drinking, and had more heavy drinking days, however those with co-occurring illnesses reported more drinking-related symptoms. Within the PTSD group, combat exposure was associated with increased drinking independent of the severity of PTSD symptoms. This study underscores the importance of screening for comorbidity in clinical treatment settings, and for collecting detailed drinking histories and assessment of psychiatric symptoms across all domains of psychopathology.

Other related publications and presentations:

1. At the Research Society of Alcoholism meeting in Orlando, Florida (June, 2013) additional data was presented from a companion laboratory study to this study which evaluated the relationship between stress and drinking. Veterans diagnosed with PTSD+AD were compared to veterans and non-veterans with AD diagnosis on their reactions to stressful stimuli using a laboratory paradigm. The data showed that those with dual diagnosis had significantly stronger reactions to stress than those with diagnosis of AD alone.
2. A poster was presented at the Research Society of Alcoholism meeting in Atlanta, GA (June, 2011) comparing demographic characteristics of patients with dual diagnosis of AD and PTSD (from this study) and patients with only AD diagnosis (who had enrolled in another pharmacotherapy study) who also participated in a stress reactivity laboratory study. The findings indicated that: a) Changes in peak stress response was significantly correlated with changes in heavy drinking – the bigger the change in stress response the bigger the change in heavy drinking. b) Individuals were characterized as high stress responders (HSR) vs. low stress responders (LSR). HSR's had an overall smaller change in their drinking behavior compared to LSR's and this change was mediated by medication treatment. Specifically, a prazosin effect on alcohol drinking was the strongest in the LSR group.
3. The PI gave a presentation at the American Psychiatric Association Annual meeting on the comorbidity of PTSD and alcohol dependence in 2009. An abstract was also submitted for the Military Health Research Forum. Analysis of the data for this poster, conducted early on in the study, revealed that the two groups were very similar in terms of their demographic characteristics. There were no differences in age, gender, marital status, education, employment status, or yearly income but there were significant differences in ethnicity ($p=0.017$ Also all participants (100%) with PTSD and AD were veterans while the sample of participants with AD alone consisted of 68% veteran population.

CONCLUSION: The study is complete. We are pleased to report that the manuscript is ready for submission. We enclose it for your records and will send the final manuscript after acceptance.

REFERENCES: See the attached manuscript.

APPENDICES: Manuscript and Tables.

Prazosin for Veterans with Post Traumatic Stress Disorder (PTSD) and Co-Morbid Alcohol Dependence: A Clinical Trial

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Abstract

Posttraumatic stress disorder (PTSD) is an important and timely clinical issue particularly for combat veterans. Few pharmacologic options are available to treat PTSD, particularly among military personnel, and they are not based on rational neurobiology. The evidence for noradrenergic dysregulation underlying PTSD is compelling and the alpha-adrenergic agonist prazosin is one of the most promising medications to treat sleep disturbances associated with PTSD as well as PTSD symptoms among both veterans and civilians. Given the high rates of comorbid alcohol use disorders among those with PTSD, testing any medication in development for PTSD in individuals with comorbidity is of high clinical importance. Recent evidence suggests prazosin may also be effective in treating alcohol dependence, so its use for individuals with comorbid PTSD and alcohol dependence is compelling.

Methods: 96 veterans with PTSD and comorbid alcohol dependence were randomized to receive prazosin (16 mg) or placebo in an outpatient, randomized, double blind, clinical trial for 13 weeks. Main outcomes included symptoms of PTSD, sleep disturbances, and alcohol use.

Results: Symptoms of PTSD improved over time, but contrary to the hypothesis, there was no medication effect on PTSD symptoms, or on sleep. Alcohol consumption also decreased over time, but there were no significant differences in outcomes between medication groups.

Conclusions: Prazosin was not effective in treating PTSD symptoms, improving sleep or reducing alcohol consumption overall in this dually diagnosed group. This does not support the use of prazosin in an actively drinking population and suggests that the presence of a comorbid condition affects the efficacy of this medication. This study highlights the importance of conducting clinical trials in "real world" patients, as results may vary based on comorbid conditions.

Introduction

Post-traumatic stress disorder (PTSD) is a serious mental disorder associated with significant morbidity and mortality. The disorder is a public health issue particularly among military personnel who have served in the recent conflicts. The risk of developing PTSD among combat-exposed military personnel is very high[1] and screenings of soldiers returning from the recent conflicts in Iraq and Afghanistan have found rates of PTSD up to 24.5%.[1-4] This is also an issue for the Veterans Health Administration (VHA), where veterans are increasingly presenting for treatment; among veterans treated in the VHA, nearly 605,000 veterans were treated for PTSD in FY'11, representing 10.6% of all veterans treated by VHA.[5] By comparison, in FY 2003, 224,000 veterans were treated for PTSD; this represents a 3-fold increase over the past 8 years.

The serotonergic reuptake inhibitors (SRI) paroxetine and sertraline are first line medications and the only medications approved by the Food and Drug Administration (FDA). However, their efficacy is modest at best, and they are less effective for combat veterans than for civilian trauma survivors. [6] SSRIs have limited efficacy in the treatment of PTSD for a number of potential reasons. As noted by Friedman (2013), SSRIs are too nonspecific (i.e. many different 5HT receptor types, some with agonist and others with antagonist actions); they address a transdiagnostic irregularity in 5HT function rather an irregularity in 5HT function that is specific to PTSD; and they were chosen because they are effective in other disorders such as major depression and panic disorder. That is, the decision to conduct clinical trials using SSRIs was not based on an understanding of neurobiological abnormalities specific to PTSD.

In contrast, the use of adrenergic agents to treat PTSD represents a rational approach based on preclinical and clinical neurobiological findings. The noradrenergic system is thought to play an integral role in the development and maintenance of PTSD[7,8] The data from both preclinical and clinical studies are compelling and include evidence for heightened physiologic responsivity to trauma-related cues, elevated 24-hour urinary noradrenaline (NE) excretion, increased 24-hour plasma NE, increased CSF NE , decreased platelet alpha-2 adrenergic receptor number, reduced norepinephrine transporter availability in the locus coeruleus, and exaggerated subjective, behavioral, cardiovascular and

biochemical responses to the alpha adrenergic antagonist, yohimbine. These data have linked exaggerated noradrenergic reactivity is related to a number of trauma-related symptoms including hypervigilance, exaggerated startle response, irritability, aggression, intrusive memories and nightmares. Thus, reducing NE activity represents a rational approach to treating PTSD.

To date, a number of adrenergic agents have been tested for their efficacy in treating PTSD. Clonidine and guanfacine are alpha 2 adrenergic agonists that suppress the release of NE via actions at the pre-synaptic alpha-2 autoreceptor, Propranolol is a non-selective beta-adrenergic agent that reduces the effects of NE by blocking postsynaptic B1 and B2 receptors. Prazosin is an alpha-1 adrenergic receptor antagonist that blocks the actions of NE on alpha 1 receptors. Preclinical data would predict that alpha-1 blockade in the locus coeruleus,[9] amygdala,[10] thalamus,[11] and prefrontal cortex[12] would help to preserve prefrontal cortical function and reduce hypervigilance, insomnia, intrusive memories, sleep disturbances and nightmares in humans suffering with PTSD.

The alpha -2 receptor agonists clonidine and guanfacine have demonstrated limited efficacy for the treatment of PTSD, although larger clinical trials are needed. Similarly, there are no large randomized placebo controlled trials of beta-blockers for the treatment of PTSD, although several studies have assessed the effects of beta-blockers on memory consolidation if administered immediately following a traumatic event. The most promising medication is prazosin, and since 2003, there have been four randomized placebo-controlled trials of prazosin which include combat veterans with PTSD. All four trials, with subject numbers ranging from 10 to 67, reported a significant reduction in daytime hyperarousal, nightmares and global clinical status. In the largest and most recent of these trials, a significantly greater reduction in total score of the Clinician Administered PTSD Scale (CAPS) was also observed for the group taking prazosin compared to placebo. A large multisite cooperative study evaluating prazosin for the treatment of PTSD symptoms, insomnia and nightmares in veterans has recently been completed, but results have not yet been published. Of note, veterans with alcohol dependence were excluded in that study. [13] The success of prazosin, a theory-driven rational pharmacological intervention for PTSD, has been greeted with enthusiasm by clinicians and researchers, and led to its inclusion in the Department of Veterans

Affairs and Department of Defense Treatment Guidelines for PTSD as a recommended adjunctive treatment for sleep/nightmares in trauma survivors with PTSD.

The lack of effective pharmacotherapies to treat PTSD is even more glaring when considering those individuals who have a concurrent alcohol use disorder. A recent Institute of Medicine Report has highlighted the alarmingly high rate of substance abuse (including alcohol) among servicemen and women and how it undermines military readiness.[14] It is therefore not surprising that alcohol use disorders (AUD), including alcohol dependence (AD) are prevalent among military personnel and are associated with substantial medical, psychiatric, and economic impact.[15-18] This is a growing problem as a new cohort of Iraq and Afghanistan combat veterans report high rates of alcohol and substance abuse. There is a high rate of comorbidity between PTSD and alcohol use disorders, and co-occurring disorders are associated with worse treatment outcome than either disorder alone[19], including higher rates of psychosocial and medical problems and higher utilization of inpatient hospitalization, functional deficits[20] and significantly lower quality of life.[21] Few studies have evaluated treatments in those with active comorbid conditions.

Noradrenergic systems have also been implicated in excessive alcohol use, including findings of increased noradrenergic activity during early withdrawal and protracted abstinence in both preclinical and clinical studies.[22] This cycle of withdrawal and early abstinence is also related to increased negative emotion and stress, suggesting medications targeting noradrenergic function might be particularly helpful in treating comorbidity. After preclinical evidence suggested prazosin may be useful in attenuating drinking behavior[23], prazosin was tested in a pilot study as a treatment of AD.[7] Results suggested prazosin was superior to placebo in decreasing drinking quality and frequency. Ongoing studies are underway, including a larger clinical trial of prazosin in alcohol dependence[24] and in a controlled crossover pilot trial to test the hypothesis that prazosin may reduce cocaine and alcohol cravings in substance dependent veterans. [25]

At least some studies suggest noradrenergic agents may be effective in the treatment of comorbidity. In work by our group, the noradrenergic antidepressant, desipramine, was as effective as the Food and Drug Administration (FDA)-

approved serotonergic antidepressant sertraline in treating PTSD, and more effective than sertraline for alcohol use outcomes.[26] In this study, we wished to test the hypothesis that prazosin would be an effective medication in treating both symptoms of PTSD and sleep as well as alcohol consumption among veterans with PTSD and comorbid alcohol dependence.

Methods

This study was approved by the Human Subjects Subcommittees of the VA Connecticut Healthcare System (West Haven, CT) the Bedford VA Medical Center (Bedford, MA), and by the Yale Human Investigations Committee (New Haven, CT). The participants (n=96) were veterans who were patients from West Haven and Bedford VAs (n=41 from CT, and n=55 from MA). After signing informed consent, potential participants, were evaluated and included if they were men or women, ages of 21-65, met DSM-IV criteria for current PTSD and alcohol dependence (AD) (determined by structured clinical interview)[27], and who reported at least one episode of heavy drinking over the past 14 days. Subjects were medically healthy by physical and laboratory examination, and for females, not pregnant and using adequate birth control. Exclusion criteria included unstable or current serious psychotic symptoms, such as suicidal or homicidal ideation, or medical problems that would contraindicate the use of prazosin. Subjects could not be taking medications thought to influence alcohol consumption (such as naltrexone, disulfiram or acamprosate), but other psychiatric medications were allowed. Subjects were also required to be abstinent for 2 days prior to randomization (see Figure 1).

Treatments:

After providing written informed consent, subjects completed an intake assessment, which included a physical examination, laboratory assessments, diagnostic and psychiatric evaluation. Following completion of baseline assessments, 96 subjects were randomized to one of two groups for 13-weeks. Randomization included prazosin 16mg per day or placebo in a double-blind fashion. Prazosin was titrated upward during the first 2 weeks, starting at 2mg per day and then increased over the 2 weeks to 16 mg per day in divided doses. Study medications were dispensed in blister packs. Medication compliance was monitored at every visit for each blister pack. All subjects also received Medical Management therapy[28] administered by a trained research nurse.

Assessments:

Baseline Measures: After signing informed consent, all subjects completed an intake assessment. After laboratory examination subjects were then screened using the SCID-I to be sure they met eligibility criteria and to establish accurate diagnoses, which were confirmed by a psychiatrist. A routine medical evaluation was performed including medical history, physical exam, and an EKG. Alcohol Dependence Severity (ADS)[29], Obsessive-Compulsive Drinking Scale (OCDS)[30], and Timeline Follow Back (TLFB)[31] were used to assess measures of alcohol use, craving and consequences.

Outcome Measures: Primary outcomes were measures of PTSD severity, alcohol use and sleep disturbances. PTSD symptom severity was assessed every four weeks by the *Clinician Administered PTSD Scale for DSM-IV* (CAPS)[32]. The *Timeline Follow-Back Interview* [31] was administered by highly trained research personnel at each weekly visit to collect a detailed self-report of daily alcohol and other substance use throughout the 84-day treatment period as well as for the 90-day period prior to randomization. Alcohol consumption was confirmed using serum gamma-glutamyl transferase (GGT), collected 4 times during the study (baseline, week4, week8 and week12). Craving was assessed weekly using the *Obsessive Compulsive Drinking and Abstinence Scale* (OCDS)[30]. Sleep was

measured weekly using the Pittsburgh Sleep Quality Index[33] and 2 questions from the CAPS, recurrent distressing dreams, and difficulty falling/staying asleep.

Side effects and common adverse symptoms were evaluated by the research nurse weekly using a modified version of the *Systematic Assessment for Treatment Emergent Events* (SAFTEE).[34] The symptoms that are known to be associated with treatment with prazosin were specifically screened for on a weekly basis. The symptoms were then clustered into the following categories: gastrointestinal, central nervous system, general, dermatological, genitourina, cardiovascular, ophthalmological, and musculoskeletal.

Data Analysis:

Descriptive statistics were used to summarize the data on all randomized subjects. All continuous variables were examined for adherence to the normal distribution using normal probability plots and Kolmogorov-Smirnov tests. The alcohol data was not normally distributed. Log transformations were applied but normality was not achieved. Therefore, the alcohol data were ranked and nonparametric tests for repeated measures analysis were used.[35] Baseline demographic characteristics for the two treatment groups (prazosin vs. placebo) were compared using chi-square tests for categorical variables, and using analysis of variance (ANOVA) for continuous variables. The analyses were on the intent-to-treat sample. All analyses were performed using 19.0 Version of SPSS. All statistical testing was at a two-tailed alpha level of 0.05. Bonferonni adjustments were applied to the analysis of CAPS subscales (3 subscales; α=0.016), the alcohol data (6 drinking outcome measures; α=0.008), craving data (2 subscales: α=0.025) and the comparison of side effects (8 symptom groups; α=0.006).

The outcome variables included: a) PTSD symptoms (CAPS total scores and CAPS subscales); b) measures of alcohol consumption (percent of subjects who abstained from heavy drinking; average number of drinks per week, number of drinking days, number of heavy drinking days, consecutive days of abstinence and number of drinks per drinking day) and craving (OCDS scores and subscales), and c) changes in sleep (PSQI sleep quality index, CAPS recurrent distressing dreams, and CAPS difficulty falling/staying asleep). Mixed effects models were used to assess changes in PTSD symptoms, alcohol consumption and sleep over time. We

selected the best-fitting variance-covariance structure based on Schwartz-Bayesian Information Criterion (BIC). The treatment comparisons and site were between-subject factors in the models and time (12 weeks) was used as a within-subject factor (when applicable). The use of the mixed-effects models approach for the analysis of our data has several specific advantages. Unlike traditional repeated measures analyses, mixed effects models allow for different numbers of observations per subject, use of all available data on each subject and are unaffected by randomly missing data. They also provide flexibility in modeling the correlation structure of the data.[36]

Results

Demographic variables: Ninety-six veterans participated in this study. As shown in Table 1, the sample was primarily male (94%), Caucasian (81%), separated/divorced (44.5%), and on average 43.98 (SD=12.96) years old (ranging in age from 22 to 64 years old). This sample of Veterans exhibited severe PTSD symptoms (mean=73.7, SD=17.86) and consisted of heavy drinkers. They averaged about 19.47 drinks per drinking day (SD=12.12) with 44.9% of those days being heavy drinking days. ADS scores (<21) indicated an intermediate level of alcohol dependence (mean=19.53, SD=8.21) among participants, a level often associated with psychological problems related to drinking. There were no significant differences between those who were randomized to prazosin vs. those on placebo on any demographic or clinical variables (see Table 1).

Dosing and Retention: The titration for prazosin was according to a predetermined schedule over 2 weeks starting at 1mg once a day and reaching 16 mg twice a day by the beginning of the third week (day 15). Prazosin was well tolerated with 58% of subjects reaching the 16mg dose within 2 weeks. The average maintenance dose of medication was 14.5 mg (SD=3.14). In this study 78.1% of the subjects completed the study (75/96). Completers were defined as subjects for whom we had complete data at the end of the treatment period (week 12) whether they remained on medication or not. There was a significantly higher rate of completion in the prazosin group (43/50 or 86.0%) compared to placebo (32/46 or 69.5%) ($\chi^2_{(1)}$=3.78, p=.05). In this study, 56.3% of the subjects (54/96) remained on study medication for 12 weeks. There was no difference in the medication dropout rate between the treatment groups (20/50 or 40.0% in the

prazosin group and 22/46 or 47.8% in the placebo group) ($\chi^2_{(1)}$=0.596, p=.44). There was no difference between the groups on the average number of days in the study ($F_{1,516.49}$ =0.89, p=.34) (mean=74.9, SD=22.00 for prazosin and mean=70.1, SD=26.09 for placebo).

PTSD Outcomes: CAPS was administered at baseline, weeks 1, 4, 8 and 12. One analysis was performed using time, medication and site in the model. The analysis of total scores revealed only significant effect for time ($F_{4, 76.09}$=44.27, p=.000) and no other significant main effects, two-way or three-way interactions including time X medication group, or time X medication X site (see Table 2). Similarly, the results for the 3 subscales, including hyper-arousal, avoidance and re-experiencing showed a main effect of time, but no effect of medication, medication x time, or medication x time x site. There were no significant site effects on any of the CAPS variables (total or any of the subscales)

Sleep: The analysis of the PSQI sleep quality index revealed only a significant main effect of time ($F_{3, 66.58}$=14.84, p=.0001) and no other significant main effects or interactions. The results were similar using the CAPS distressing dreams item showing only a significant main effect for time ($F_{4, 75.61}$=26.88, p=.0001) but no other significant main effects or interactions. For the CAPS difficulty falling/staying asleep item, there was a significant main effect of time ($F_{4, 77.04}$=9.00, p=.0001) and a significant medication x time interaction ($F_{4,77.04}$=2.77, p=.03). The analysis examining whether abstinence had an effect on sleep revealed no effect on the PSQI sleep quality index ($F_{1, 82.9}$=0.474, p=.49), CAPS distressing dreams ($F_{1, 83.6}$=0.965, p=.33) or CAPS difficulty falling/staying asleep ($F_{1, 89.29}$=0.071, p=.79) (see Table 2).

Drinking Outcomes: During the treatment phase of the study there was a significant decrease in the average number of drinks over time ($F_{11,73.18}$=3.64, p=.0001), but no significant effect of medication. This was confirmed by GGT levels that significantly declined over time (baseline, week 4, week 8 and week 12) ($F_{4, 66.22}$=7.30, p=.0001). There were no significant differences in GGT levels based on medication assignment (p=.39) or medication by time interaction (p=.17). There was also no medication effect on the number of drinking days ($F_{1, 80.3}$=0.294,

p=.58), on the number of heavy drinking days ($F_{1, 33.17}$=0.202, p=.65), on consecutive days of abstinence ($F_{1, 3221.2}$=3.64, p=.05) and on the number of drinks per drinking day ($F_{1, 72.09}$=1.358, p=.24). In this sample, 52% of subjects were heavy drinkers overall, defined as having 5 or more drinks on one occasion; there was no significant difference in percentage of heavy drinkers between the medication groups (54.7% [placebo] vs. 51.0% [prazosin] of heavy drinkers) ($\chi^2_{(1)}$=0.13, p=.72). In this study, 39/96 (41%) of subjects abstained from drinking throughout the trial. In the prazosin group, 23/50 (46%) subjects abstained from drinking throughout the trial while in the placebo group only 16/46 (34.8%) abstained from drinking. However, these numerical differences did not reach statistical significance ($\chi^2_{(1)}$=1.25, p=.26) (see Table 2).

There were significant site differences on some drinking outcomes, including consecutive days of abstinence ($F_{1, 18100.15}$ =20.48, p=.000), and on number of drinking days ($F_{1, 3914.37}$=14.33, p=.000), but not on number of drinks per week over time ($F_{1, 55.41}$=2.79, p=.10), percentage of subjects with heavy drinking ($F_{1, 2058.75}$ =6.63, p=.01), drinks per drinking days ($F_{1, 3.63}$=0.068, p=.79) or heavy drinking days ($F_{1, 1056.15}$=6.44, p=.01). Also, there were no significant interactions involving site for any of the drinking variables.

Craving: Craving for alcohol was assessed using the OSDS total score including the two subscales. For the total OCDS there was a significant main effect for time ($F_{12, 59.8}$=6.92, p=.0001), a non-significant medication effect ($F_{1, 88.9}$=0.40, p=.52), and a non-significant time X medication interaction ($F_{12, 59.8}$=1.89, p=.05) (see Table 3). The results were similar for each of the subscales, including obsessions and compulsions, and there was no effect of site on craving.

Adverse Events/ Side Effects: The most frequently reported adverse event (AE) was alcohol relapse. Twelve subjects in this study were either seen in the emergency room or hospitalized briefly for alcohol relapse (five of those subjects were receiving prazosin and 7 were receiving placebo). One subject (placebo) reported homicidal ideation after 7 doses; he discontinued from the study for other (time commitment) reasons. None of these AE's were thought to be related to study medication or participation.

There were six medically-related AEs (all participants were on active medication). Four AE's were determined to be unrelated to study medication/participation: partial thrombus, chest pain appendicitis; all were not study related and subjects completed the study. There were three AE's that were thought to be study related and these included an episode of fainting (subject discontinued treatment); and two incidents of falling (one subject completed treatment while the other dropped out). There were two other incidents reported to the HSS. In one case the "medication blind" envelope was not properly filed and in the other the wrong medication was dispensed (both subjects on placebo).

There was no difference between the medication groups on the overall rate or frequency of side effect reporting. Analysis of individual symptoms most frequently reported with prazosin – dizziness, dizziness when standing up and loss of balance revealed a non-significant medication effect for dizziness ($F_{1, 27.8}$=3.92, p=.05 after a Bonferonni adjustment) although subjects on prazosin reported this symptom more frequently than those on placebo. There were no other significant findings in the reporting on symptoms.

Discussion

The findings from this study suggest that, while subjects as a group showed improvement in measures of sleep and symptoms of PTSD over time, there was no advantage of prazosin over placebo in treating symptoms of PTSD or sleep disturbance. Further, while subjects overall reduced their drinking, there was no advantage of prazosin over placebo in any of the drinking related outcomes. These results are in contrast with most of the data on prazosin suggesting that it is effective, particularly in attenuating sleep disturbance but also in improving some symptoms of PTSD among those without comorbid alcohol dependence.

The results are unexpected in that prazosin was not effective in ameliorating sleep disturbances, including nightmares in this population. There is a growing body of literature supporting its efficacy including a meta-analysis suggesting prazosin has a moderate effect size and is comparable to other non-pharmacologic interventions. [37] Further, the attenuation of sleep disturbance seems to be related to an improvement in PTSD symptoms.[38] There are several possible explanations for why prazosin was not more effective than placebo in ameliorating sleep

disturbances and treating symptoms of PTSD in this study. The lack of efficacy may represent the effect of on-going alcohol consumption in interfering with prazosin's effect. Alcohol has a clear effect on sleep architecture, affecting maintenance of sleep and REM sleep, particularly at high doses of alcohol.[39] After alcohol is metabolized, during the later hours of the night, there can be a rebound effect of REM sleep, the period in which dreaming occurs. This would suggest that prazosin may not be an effective medication to treat sleep disturbances particularly during early abstinence.

Whether alcohol interferes with prazosin effects in treating PTSD symptoms, or whether this is a severity issue is unclear, since there is evidence to suggest that those with co-occurring illness had significantly worse psychopathology across all domains[40] and since, individuals with PTSD who use alcohol and drugs to control symptoms of PTSD are more likely to have other symptoms of psychopathology and lower quality of life than those who do not use substances. [41] It should be stated that prazosin's effectiveness for PTSD has not been definitively established. While previous studies with prazosin were promising, this negative study represents the largest study published to date (n=95). The VA Cooperative[42] evaluating prazosin for PTSD among veterans was recently completed but the results have not yet been reported; the results from this study should shed light on this question.

The results from this study also do not support the use of prazosin as an agent for preventing relapse and decreasing alcohol consumption in this group of subjects. There was no evidence, from any of the drinking outcomes, that prazosin had any effect on drinking or craving measures. These results are in contrast to several recent studies: a laboratory study suggesting prazosin attenuated stress and cue induced craving for alcohol in alcohol dependent individuals[43] and a recently completed small clinical trial of prazosin study in comorbid individuals (those with PTSD and comorbid AD) which suggested prazosin was effective in treating alcohol use but not PTSD (Simpson, personal communication). It should be noted that alcohol consumption significantly decreased over time and there was a high rate of abstinence in this study. This might be due to the close follow up and support by the research team, which may have overwhelmed any potential medication effect. There is evidence of a high placebo effect in alcohol pharmacology trials[44], which has been commented about in terms of the naltrexone

literature. Further, in this study, the site differences were more robust than the medication effects. The higher rates of abstinence in the Massachusetts site may reflect the nature of the programs which include a residential treatment program, suggesting that environmental factors outweigh medication effects for this group of patients.

Limitations include that the study was conducted with primarily male veterans and results may not be generalizable to other populations. Further, the dose and the medication taper were set by the research protocol, and not adjusted for symptoms as is done in clinical practice. It is possible that lower doses would have been more effective. Finally, the psychosocial treatments offered may have overwhelmed any medication effect, as was evidenced by the site differences with better outcomes from settings that provided a substance-free environment. Nevertheless, this study is the largest study reported to date in a veteran population evaluating the use of medication for a comorbid group of patients.

In this study we investigated the effect of prazosin on symptoms of sleep and PTSD among veterans with co-occurring PTSD and AD. This results do not provide support for its use as a medication in actively drinking individuals to treat PTSD or to prevent alcohol consumption. The study does highlight the importance of conducting studies in those with comorbidity, as many studies establishing efficacy for medications are conducted in subjects who do not adequately resemble the "real world" patients in clinical practice.

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Figure 1. Consort Table

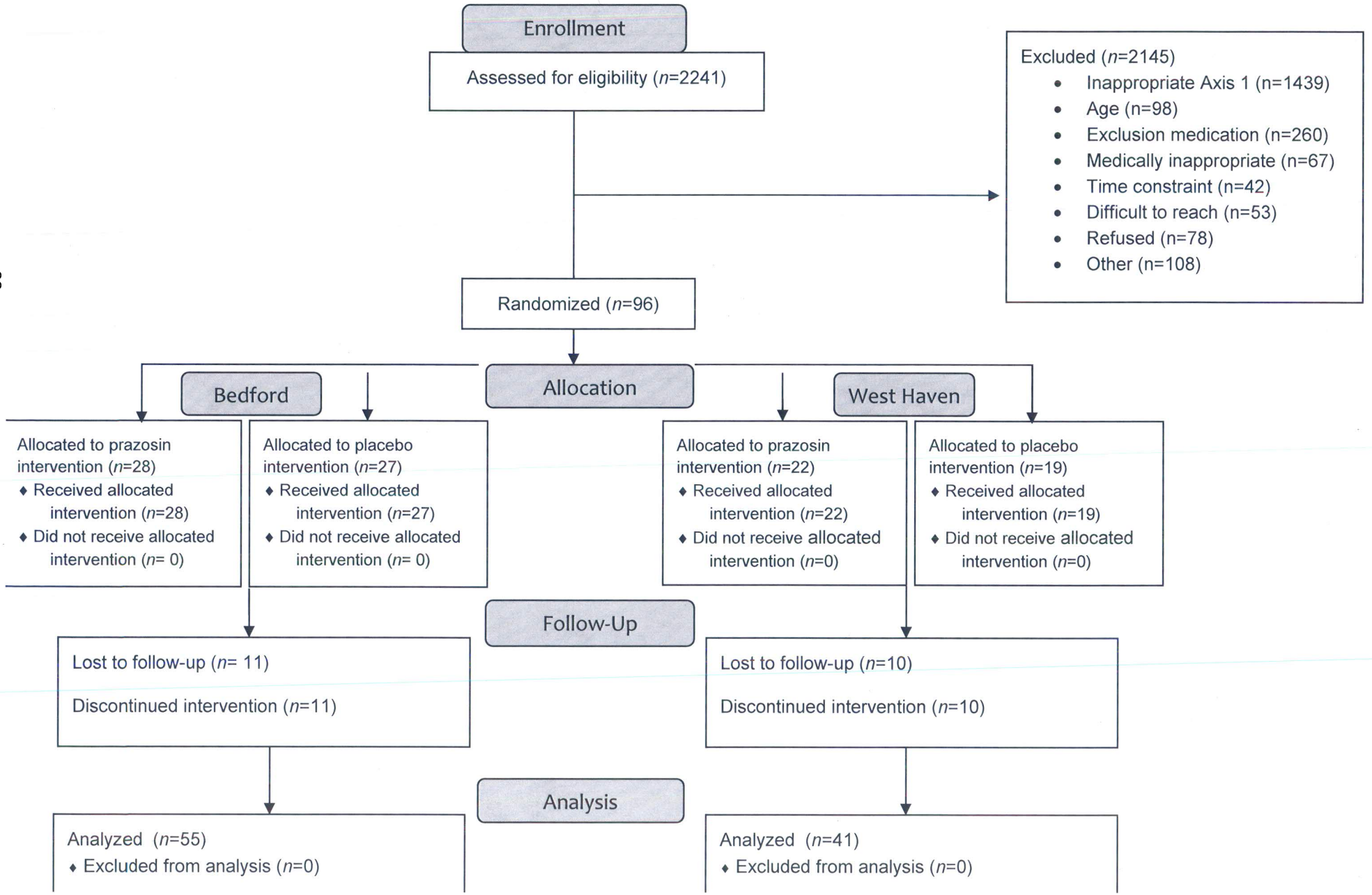

Table 1. Demographic characteristics of veterans who were assigned to either prazosin or placebo

Variables	Prazosin n=50	Placebo n=46	Statistics
Demographic Characteristics			
	mean (sd)	*mean (sd)*	***F*, p**
Age	44.50 (13.20)	43.40 (12.95)	.169, .682
Gender	*n (%)*	*n (%)*	**X^2, p**
Male	46 (92.00)	43 (95.56)	.506, .477
Female	4 (8.00)	2 (4.44)	
Ethnicity			
Caucasian	40 (80.00)	38 (82.60)	2.796, .247
African American	7 (14.00)	7 (15.21)	
Other	3 (6.00)	0	
Marital Status			
Single	16 (32.600)	13 (28.26)	2.124, .547
Married/cohabitating/partner	10 (20.00)	11(23.91)	
Separated/divorced	22 (44.00)	21 (45.65)	
Widowed	2 (4.00)	0	
Demographic Characteristics			
CAPS			***F*, p**
Severity of PTSD symptoms	71.86 (20.32)	75.86 (14.44)	1.16, .284
Re-experiencing	19.62 (8.22)	21.14 (7.23)	.890, .348
Hypervigelence	22.94 (7.37)	22.52 (6.15)	.087, .768
Avoidance	29.30 (9.04)	31.76 (7.08)	2.098, .151
Measures of Alcohol Consumption			
# Drinking days (over 90 days)	47.02 (29.87)	43.11 (27.79)	.433 .512
Heavy drinking days(over 90 days)	41.30 (29.34)	39.51 (28.2)	.091, .763
Drinks per drinking day	17.33 (10.73	21.90 (13.24)	3.410, 068
Percent drinking days	45.89 (32.60)	43.90 (31.36	.091, .763
Total ADS	18.94 (6.86)	20.20 (9.54)	.555, .458

Table 2. Means and standard deviations for PTSD symptoms and sleep

		Prazosin Mean (SD)	Placebo Mean (SD)	F, p
CAPS	**Total**			Drug 0.04, 0.84
	Baseline	71.86 (24.65)	75.71 (26.36)	Time 54.31, 0.00
	Week 12*	37.94 (37.62)	37.93 (41.13)	Drug x Time 1.72, 0.16
	Re-Experience			Drug 0.19, 0.67
	Baseline	29.30 (10.79)	31.76 (11.44)	Time 45.15, 0.00
	Week 12*	15.57 (12.67)	14.89 (13.93)	Drug x Time 1.68, 0.16
	Avoidance			Drug 0.02, 0.90
	Baseline	19.62 (11.32)	20.99 (12.13)	Time 44.27, 0.00
	Week 12*	10.41 (16.76)	8.87 (18.59)	Drug x Time 2.21, 0.08
	Hyperarousal			Drug 0.41, 0.52
	Baseline	22.94 (9.46)	22.44 (10.04)	Time 25.80, 0.00
	Week 12*	15.65 (13.87)	14.84 (15.09)	Drug x Time 1.47, 0.22
Sleep	**PSQI**			Drug 0.05, 0.82
	Baseline	21.47 (0.94)	22.80 (0.97)	Time 14.85, 0.00
	Week 12*	17.05 (1.31)	16.76 (1.45)	Drug x Time 0.62, 0.60
	CAPS Difficulty			Drug 0.26, 0.87
	Baseline	4.69 (0.31)	4.77 (0.32)	Time 9.00, 0.00
	Week 12*	2.50 (0.38)	2.41 (0.41)	Drug x Time 2.77, 0.03
	CAPS Recurrent			Drug 0.02, 0.88
	Baseline	5.92 (0.32)	5.44 (0.34)	Time 26.89, 0.00
	Week 12*	4.25 (0.46)	4.91 (0.50)	Drug x Time 0.30, 0.88
Drinking	**Number Drinking Days**			
	Baseline	47.02 (29.87)	43.11 (27.79)	Drug 0.29, 0.59
	Active Treatment Phase	11.04 (18.86)	9.21 (16.64)	
	Heavy Drinking Days			
	Baseline	41.30 (29.34)	39.51 (28.20)	Drug 0.20, 0.65
	Active Treatment Phase	7.16 (13.78)	6.05 (12.56)	
	Drinks per Drinking Day			
	Baseline	17.33 (10.73)	21.90 (13.24)	Drug 1.36, 0.25
	Active Treatment Phase	4.44 (5.71)	6.91 (9.12)	
	Consec Days Abstinence			
	Baseline			Drug 0.00, 0.96
	Active Treatment Phase	49.71 (34.74)	48.86 (31.94)	
Craving	**OCDS Total**			Drug 0.40, 0.53
	Baseline	17.36 (1.77)	19.86 (1.89)	Time 6.92, 0.00
	Week 12*	10.12 (1.41)	6.70 (1.58)	Drug x Time 1.89, 0.05